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FILE CONTENT:1840 - 14 Dec 2010 VOL 153 ISS 25

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=> d que sta l4
L2              STR
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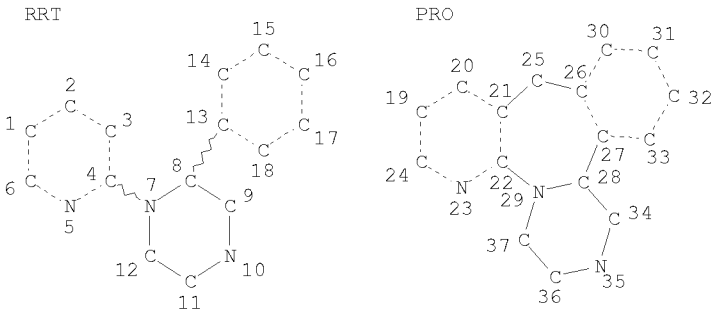


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  37

STEREO ATTRIBUTES: NONE
L4           24 SEA FILE=CASREACT SSS FUL L2 (    74 REACTIONS)

100.0% DONE      74 VERIFIED      74 HIT RXNS                      24 DOCS
SEARCH TIME: 00.00.01


=> d bib abs crd l8 tot
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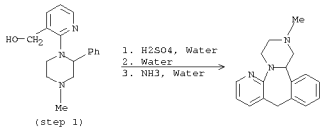
L8 ANSWER 1 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 152:501409 CASREACT
TI Process for the preparation of 1-(3-hydroxymethylpyrid-2-yl)-2-phenyl-4-methylpiperazine and mirtazapine
IN Bhanu, Manjunath Narayan; Naik, Samir; Joshi, Prashant; Sharma, Vijay
PA Watson Pharma Private Limited, India
SO PCT Int. Appl., 26pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2010046851	A1	20100429	2009WO-IB0054625	20091020
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
IN---200802279	A	20100806	2008IN-000002279	20081022
PRAI 2008IN-000002279		20081022		

AB The invention relates to the process for the manufacture of mirtazapine and intermediates useful in preparing mirtazapine. Mirtazapine was prepared via hydrolysis of 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine; the resulting 1-(3-carboxypyridyl-2)-4-methyl-2-phenylpiperazine underwent reduction to give 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenylpiperazine, which underwent cyclization to give the title compound

RX(3) OF 6

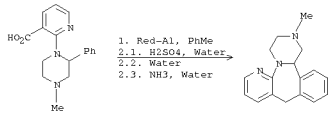


(step 1)

CON: STAGE(1) room temperature -> 15 deg C; <20 deg C; <20 deg C -> 30 deg C; 12 hours, 25 - 30 deg C
STAGE(3) <30 deg C, pH 10 - 11

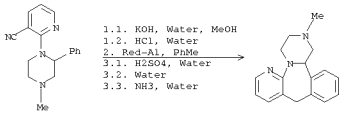
L8 ANSWER 1 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(5) OF 6 - 2 STEPS



CON: STEP(1.1) room temperature -> 15 deg C; - 2 hour, 15 - 20 deg C; 20 deg C -> 25 deg C; 5 hours, 25 - 30 deg C
STEP(2.1) room temperature -> 15 deg C; <20 deg C; <20 deg C -> 30 deg C; 12 hours, 25 - 30 deg C
STEP(2.3) <30 deg C, pH 10 - 11

RX(6) OF 6 - 3 STEPS

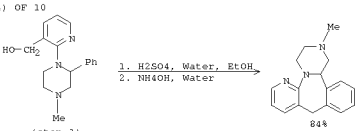


CON: STEP(1.1) room temperature -> 90 deg C; 24 hours, 85 - 90 deg C; 90 deg C -> 50 deg C
STEP(1.2) pH 7
STEP(2.1) room temperature -> 15 deg C; - 2 hour, 15 - 20 deg C; 20 deg C -> 25 deg C; 5 hours, 25 - 30 deg C
STEP(3.1) room temperature -> 15 deg C; <20 deg C; <20 deg C -> 30 deg C; 12 hours, 25 - 30 deg C
STEP(3.3) <30 deg C, pH 10 - 11

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 152:429664 CASREACT
TI Improved synthesis of mirtazapine
AU Guo, Manfang; Bao, Lixin; Yin, Zhengyuan; Cui, Tingxiu; Liu, Dan
CS Medisan Pharmaceutical Co., Ltd., Harbin, Heilongjiang Province, 150025, Peop. Rep. China
SO Zhongguo Yaowu Huaxue Zazhi (2008), 18(5), 350-352
CODEN: ZYHZEF; ISSN: 1005-0108
PB Zhongguo Yaowu Huaxue Zazhi Bianjibu
DT Journal
LA Chinese
AB The synthetic procedure of antidepressant mirtazapine [i.e., 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine] was improved. Using 2-chloronicotinonitrile and 1-methyl-3-phenylpiperazine as the starting materials, mirtazapine was obtained by a synthetic sequence involving an alkylation, hydrolysis, reduction and intramol. Friedel-Crafts alkylation. The structure of mirtazapine was confirmed by elemental anal., IR, NMR, 13C-NMR, MS. Compared with the synthetic process reported in the literature, the above-mentioned optimized synthetic procedure was simple and suitable for industrial production with lower cost and higher yield. The overall yield was improved from 46% to 60%.

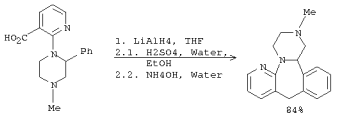
RX(4) OF 10



(step 1)

NOTE: 60% yield over 4 steps from 3-Pyridinecarbonitrile, 2-chloro- and Piperazine, 1-(3-methylphenyl)-
CON: STAGE(1) room temperature; 2 hours, room temperature
STAGE(2) pH 9

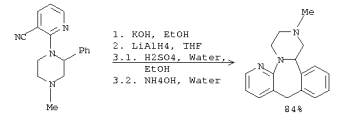
RX(7) OF 10 - 2 STEPS



NOTE: 2) 60% yield over 4 steps from 3-Pyridinecarbonitrile, 2-chloro- and Piperazine, 1-(3-methylphenyl)-
CON: STEP(1.1) room temperature; 4 hours, reflux
STEP(2.1) room temperature; 2 hours, room temperature
STEP(2.2) pH 9

L8 ANSWER 2 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(9) OF 10 - 3 STEPS



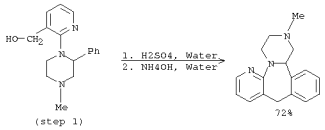
NOTE: 3) 60% yield over 4 steps from 3-Pyridinecarbonitrile, 2-chloro- and Piperazine, 1-(3-methylphenyl)-
CON: STEP(1.1) room temperature -> 100 deg C; 24 hours, 100 deg C
STEP(2.1) room temperature; 4 hours, reflux
STEP(3.1) room temperature; 2 hours, room temperature
STEP(3.2) pH 9

L8 ANSWER 3 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 152:358069 CASREACT
TI Preparation method of mirtazapine and its intermediates
IN Wan, Xinqiang; Xi, Xiaojin; Wang, Shufen; Zhong, Haitao; Li, Haibo
PA Watson Pharmaceuticals Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 11pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN---101654454	A	20100224	2009CN-010181404	20090626
PRAI 2009CN-010181404		20090626		

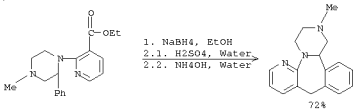
OS MARPAT 152:358069
AB This invention relates to the preparation methods of mirtazapine, 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (I), and 1-(3-alkoxycarbonyl-2-pyridyl)-4-methyl-2-phenylpiperazines (II). I is prepared by reducing II in solvent at (-10)-150°C with reducing agent. The reducing agent may be sodium borohydride, lithium borohydride, potassium borohydride, lithium aluminum hydride, and/or sodium dihydrobis(2-methoxyethoxy)aluminate, etc. II is prepared by esterifying 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine, or by reacting 2-halo-3-(alkoxycarbonyl)pyridine with 1-methyl-3-phenylpiperazine in the presence of KF, NaI, or KI. This inventive method is simple, safe, convenient, and fit for com. process.

RX(5) OF 12



CON: STAGE(1) 4 hours, 35 deg C
STAGE(2) 20 - 30 deg C, pH 8 - 9

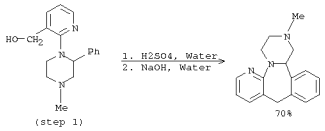
RX(9) OF 12 - 2 STEPS



CON: STEP(1.1) 4 hours, reflux; reflux -> 25 deg C
STEP(2.1) 4 hours, 35 deg C
STEP(2.2) 20 - 30 deg C, pH 8 - 9

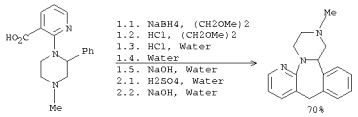
L8 ANSWER 4 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 150:121600 CASREACT
TI Synthesis of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (mirtazapine)
AU Zhang, Qingwen; Xu, Yanyan; Shi, Huilin
CS Shanghai Institute of Pharmaceutical Industry, Shanghai, 200437, Peop. Rep. China
SO Zhongguo Yiyao Gongye Zazhi (2006), 37(10), 653-654
CODEN: ZYGZEA; ISSN: 1001-8255
PB Zhongguo Yiyao Gongye Zazhi Bianjibu
DT Journal
LA Chinese
AB A method for the synthesis of the title compound is reported here. Mirtazapine was synthesized from 1-(3-carboxy-2-pyridinyl)-2-phenyl-4-methylpiperazine [i.e., 2-(4-methyl-2-phenyl-1-piperazinyl)-3-pyridinecarboxylic acid] by reduction with diborane generated in situ (sodium borohydride/HCl gas or sodium borohydride/Et2O·BF3) to provide 2-(4-methyl-2-phenyl-1-piperazinyl)-3-pyridinemethanol. A subsequent acid-mediated dehydration and cyclization of the latter provided the above-mentioned mirtazapine (60% overall yield).

RX(2) OF 3



NOTE: 60% yield over 2 steps from 2-(4-methyl-2-phenyl-1-piperazinyl)-3-Pyridinecarboxylic acid
CON: STAGE(1) 30 deg C; 7 hours, 30 - 40 deg C
STAGE(2) pH 1 - 2; pH 11

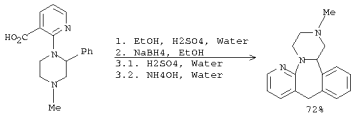
RX(3) OF 3 - 2 STEPS



NOTE: 1) alternative reaction conditions shown, 2) 60% yield over 2 steps from 2-(4-methyl-2-phenyl-1-piperazinyl)-3-Pyridinecarboxylic acid
CON: STEP(1.1) 0 - 5 deg C
STEP(1.2) 0 - 5 deg C; 5 deg C -> 60 deg C; 2 hours, 60 deg C; 60 deg C -> 0 deg C
STEP(1.3) <20 deg C
STEP(1.4) 95 deg C
STEP(1.5) pH 10
STEP(2.1) 30 deg C; 7 hours, 30 - 40 deg C
STEP(2.2) pH 1 - 2; pH 11

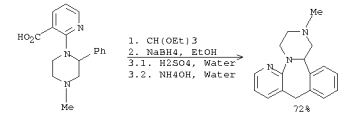
L8 ANSWER 3 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(10) OF 12 - 3 STEPS



NOTE: 1) incremental addition of ethanol and sulfuric acid
CON: STEP(1.1) 2 hours, reflux; 80 deg C; 1 hour, reflux
STEP(2.1) 4 hours, reflux; reflux -> 25 deg C
STEP(3.1) 4 hours, 35 deg C
STEP(3.2) 20 - 30 deg C, pH 8 - 9

RX(11) OF 12 - 3 STEPS

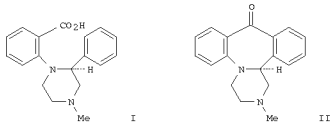


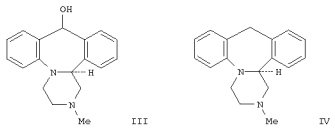
CON: STEP(1.1) room temperature -> 100 deg C; 6 hours, 100 deg C
STEP(2.1) 4 hours, reflux; reflux -> 25 deg C
STEP(3.1) 4 hours, 35 deg C
STEP(3.2) 20 - 30 deg C, pH 8 - 9

L8 ANSWER 5 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 149:471503 CASREACT
TI Method for the preparation of an enantiomer of a tetracyclic benzazepine from phenylpiperazine derivative via cyclization and reduction reactions
IN Kemperman, Gerardus Johannes
PA N.V. Organon, Neth.
SO U.S. Pat. Appl. Publ., 9pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US-20080255348	A1	20081016	2008US-000098662	20080407
PRAI 2007US-00922829P		20070411		

GI

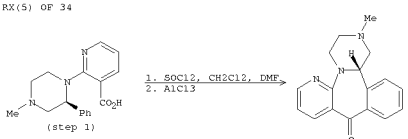




AB The present invention relates to a method for the preparation of mirtazapine and tetracyclic analogous compds. having substantial enantiomeric excess of the R or S form. The invention further relates to a novel intermediate and its use for the preparation of mirtazapine having a substantial enantiomeric excess of the R or S form. The method comprising the steps of (a): providing a carboxylic acid I having enantiomeric excess of the R or S form, (b): converting the carboxylic acid group of I into a ketone II, (c): optionally reducing II with a mild reduction agent to form the intermediate hydroxy III, (d): forming the mirtazapine IV by reduction of II or III using a strong reduction agent.

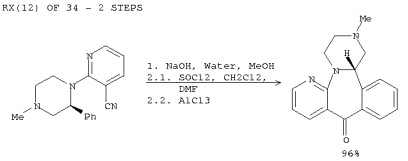
L8 ANSWER 5 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(5) OF 34



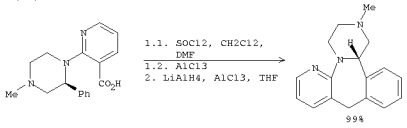
NOTE: alternative preparation shown, incremental addition, stereoselective
CON: STAGE(1) 0 deg C; 75 minutes, room temperature
STAGE(2) 8 hours, 0 deg C; room temperature

RX(12) OF 34 - 2 STEPS



NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 8 hours, 0 deg C; room temperature

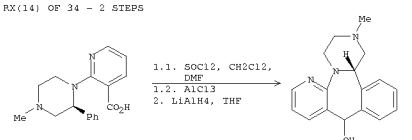
RX(13) OF 34 - 2 STEPS



NOTE: 1) alternative preparation shown, incremental addition, stereoselective, 2) stereoselective, workup
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(1.2) 8 hours, 0 deg C; room temperature
STEP(2.1) 0 deg C; 20 hours, 50 deg C

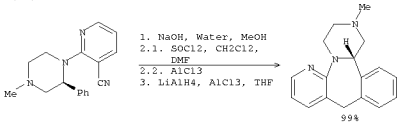
L8 ANSWER 5 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(14) OF 34 - 2 STEPS



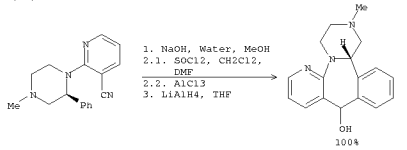
NOTE: 1) alternative preparation shown, incremental addition, stereoselective, 2) stereoselective
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(1.2) 8 hours, 0 deg C; room temperature
STEP(2.1) 0 deg C; 1 hour, room temperature

RX(21) OF 34 - 3 STEPS



NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective, 3) stereoselective, workup
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 8 hours, 0 deg C; room temperature
STEP(3.1) 0 deg C; 20 hours, 50 deg C

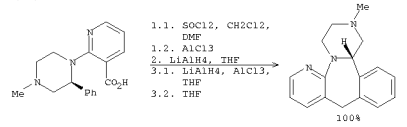
RX(22) OF 34 - 3 STEPS



NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective, 3) stereoselective
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 8 hours, 0 deg C; room temperature
STEP(3.1) 0 deg C; 1 hour, room temperature

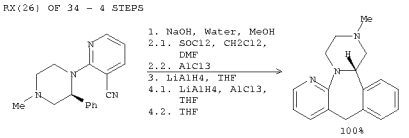
L8 ANSWER 5 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(25) OF 34 - 3 STEPS



NOTE: 1) alternative preparation shown, incremental addition, stereoselective, 2) stereoselective
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(1.2) 8 hours, 0 deg C; room temperature
STEP(2.1) 0 deg C; 1 hour, room temperature
STEP(3.1) 0 deg C; 15 minutes
STEP(3.2) 18 hours, 50 deg C

RX(26) OF 34 - 4 STEPS

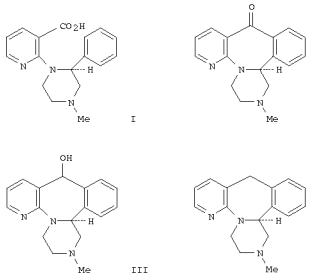


NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective, 3) stereoselective
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 8 hours, 0 deg C; room temperature
STEP(3.1) 0 deg C; 1 hour, room temperature
STEP(4.1) 0 deg C; 15 minutes
STEP(4.2) 18 hours, 50 deg C

L8 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 149:471353 CASREACT
TI Preparation of enantiomers of tetracyclic benzazepines
IN Kemperman, Gerardus Johannes
PA N.V. Organon, Neth.
SO PCT Int. Appl., 19pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2008125578	A2	20081023	2008WO-EP0054316	20080410
	WO--2008125578	A3	20081224		
	W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
	CA------2684021	A1	20081023	2008CA-002684021	20080410
	AR--------66005	A1	20090715	2008AR-000101475	20080410
	EP------2146993	A2	20100127	2008EP-000736038	20080410
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS				
	JP--2010523620	T	20100715	2010JP-000502504	20080410
	MX--2009010967	A	20091215	2009MX-000010967	20091009
	ZA--2009007537	A	20100728	2009ZA-000007537	20091027
	CN---101679431	A	20100324	2008CN-080016144	20091116
PRAI	2007EP-000105985		20070411		
	2008WO-EP0054316		20080410		

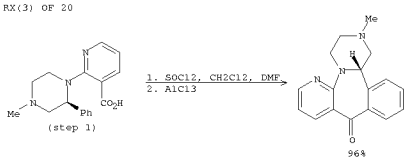
GI



AB The present invention relates to a method for the preparation of mirtazapine and tetracyclic analogous compds. having substantial enantiomeric excess of the R or S form. The method comprises the steps of (a) providing a carboxylic acid compound according to Formula I having a substantial enantiomeric excess of the R or S form, (b) converting the carboxyl group into ketone group to give ketone compound II, (c) optionally reducing ketone compound II with a mild reduction agent to form the intermediate hydroxy compound

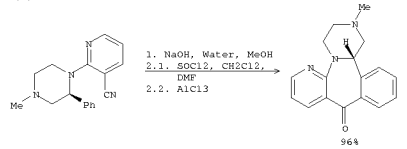
L8 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)
III, and (d) forming the mirtazapine (IV) by redn. of ketone compd. II or hydroxy compd. III using a strong redn. agent.

RX(3) OF 20



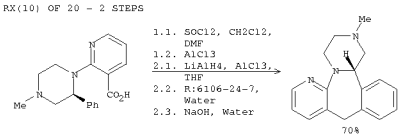
NOTE: alternative preparation shown, incremental addition
CON: STAGE(1) 0 deg C; 75 minutes, room temperature
STAGE(2) 0 deg C; 8 hours

RX(9) OF 20 - 2 STEPS



NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 0 deg C; 8 hours

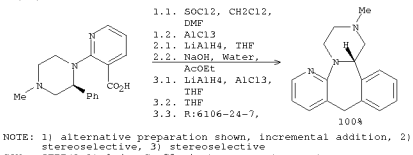
RX(10) OF 20 - 2 STEPS



NOTE: 1) alternative preparation shown, incremental addition, 2) stereoselective
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(1.2) 0 deg C; 8 hours
STEP(2.1) 0.5 deg C; 20 hours
STEP(2.2) 0 deg C
STEP(2.3) pH 14

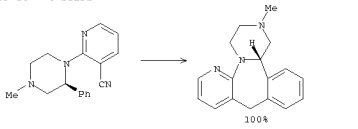
L8 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(18) OF 20 - 3 STEPS



NOTE: 1) alternative preparation shown, incremental addition, 2) stereoselective, 3) stereoselective
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(1.2) 0 deg C; 8 hours
STEP(2.1) 0 deg C; 1 hour, room temperature
STEP(2.2) pH 14
STEP(3.1) 0 deg C; 15 minutes
STEP(3.2) 18 hours, 50 deg C
STEP(3.3) 0 deg C
STEP(3.4) pH 14

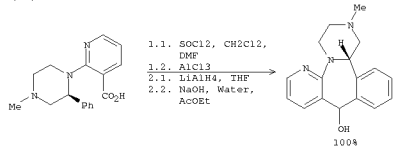
RX(19) OF 20 - 4 STEPS



NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition, 3) stereoselective, 4) stereoselective
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 0 deg C; 8 hours
STEP(3.1) 0 deg C; 1 hour, room temperature
STEP(3.2) pH 14
STEP(4.1) 0 deg C; 15 minutes
STEP(4.2) 18 hours, 50 deg C
STEP(4.3) 0 deg C
STEP(4.4) pH 14

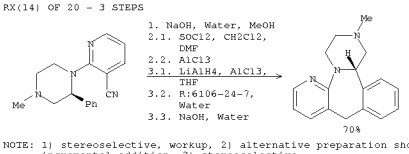
L8 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(11) OF 20 - 2 STEPS



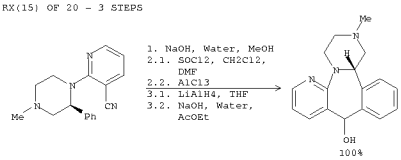
NOTE: 1) alternative preparation shown, incremental addition, 2) stereoselective
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(1.2) 0 deg C; 8 hours
STEP(2.1) 0 deg C; 1 hour, room temperature
STEP(2.2) pH 14

RX(14) OF 20 - 3 STEPS



NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition, 3) stereoselective
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 0 deg C; 8 hours
STEP(3.1) 0.5 deg C; 20 hours
STEP(3.2) 0 deg C
STEP(3.3) pH 14

RX(15) OF 20 - 3 STEPS



NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition, 3) stereoselective
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 0 deg C; 8 hours
STEP(3.1) 0 deg C; 1 hour, room temperature
STEP(3.2) pH 14

L8 ANSWER 7 OF 16 CASREACT COPYRIGHT 2010 ACS on STN

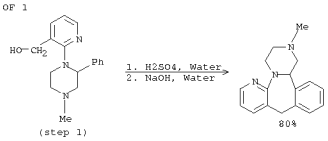
AN 149:378772 CASREACT
TI Process for production of mirtazapine
IN Maeda, Chiharu; Maeda, Takuma
PA Sumitomo Chemical Co., Ltd., Japan
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2008114691	A1	20080925	2008WO-JP0054628	20080313
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
JP--2008231062	A	20081002	2007JP-000075573	20070322
AU--2008227637	A1	20080925	2008AU-000227637	20080313
CA-----2664286	A1	20080925	2008CA-002664286	20080313
KR--20091121270	A	20091125	2009KR-007006525	20080313
EP-----2135870	A1	20091223	2008EP-000722032	20080313
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR				
CN---101541798	A	20090923	2008CN-080000740	20090313
US-20100029934	A1	20100204	2009US-000443662	20090330
PRAI 2007JP-000075573		20070322		
2008WO-JP0054628		20080313		

AB Claimed is a method for preparing mirtazapine characterized by diluting a reaction liquid [obtained by ring-closing reaction of 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-methanol (I) with concentrated sulfuric acid] with water, alkalizing the obtained diluted liquid in the presence of propanol, extracting mirtazapine into propanol, and crystallizing mirtazapine from the resulting extract Thus, I 147.4 g (0.52 mol) was added in portions over about 3 h to 98% sulfuric acid 530 g (5.4 mol) at 30°C to 40°C; the reaction mixture was stirred for about 6 h at 30°C to 40°C : a reaction liquid (677 g) was obtained; a portion of this reaction liquid (260 g) was added dropwise to water 408 g; the reaction flask was washed with 98% sulfuric acid 25.5 g which was then added to the diluted liquid; 25% aqueous NaOH solution 635.8 g was added dropwise to the diluted liquid at 13°C to 30°C to adjust the pH to 1.5. Charcoal 21 g was added to the above liquid; the resulting mixture was stirred for 45 min at 30°C to 33°C, filtered, and washed with water 108 g; the filtrate was divided into 2 portions : 2-propanol 51 g was added to one portion 699 g; 25% aqueous NaOH solution (53.4 g) was added dropwise to the above liquid to adjust the pH to 11.2; the mixture was allowed to sep. into 2 layers at about 76°C; 2-propanol 255 g was added to the organic layer : this liquid was stirred for 15 min at about 28°C with alumina A-11 (Sumitomo Chemical Co.) 4.8 g; charcoal 1.4 g was added, and the resulting mixture was stirred for 15 min; the mixture was filtered, and washing was done with 2-propanol 14.2 g; the filtrate was evaporated under reduced pressure until a concentrate (38.5 g) was obtained; 2-propanol 7.5 g was added, and the mixture was heated to 66°C; heptane 15 g was added; mirtazapine seed crystals were added at about 53°C; the resulting mixture was kept for 1 h at 50°C. The above mixture was cooled over 6 h to 1°C to give mirtazapine crystals 21.2 g (yield : 80%; purity (HPLC) : 99.98%). Mirtazapine is a known antidepressant.

L8 ANSWER 7 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(1) OF 1



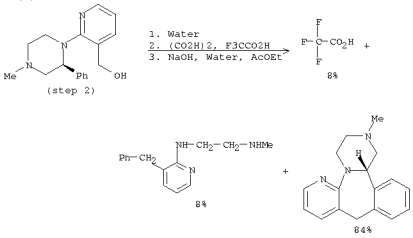
(step 1)

CON: STAGE(1) 6 hours, 30 - 40 deg C
STAGE(2) 13 - 30 deg C, pH 1.5

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

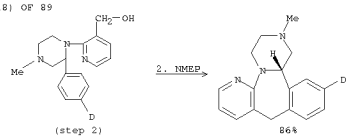
RX(7) OF 89



(step 2)

NOTE: regioselective, 3-Benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv. of polyphosphoric acid, polyphosphoric acid (PPA) used first stage
CON: STAGE(1) <140 deg C
STAGE(2) 18 hours, 130 deg C

RX(18) OF 89



(step 2)

NOTE: regioselective, alternative reaction conditions gave lower yield, polyphosphoric acid (PPA) used first stage
CON: STAGE(1) <140 deg C
STAGE(2) 100 deg C

L8 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN

AN 149:288755 CASREACT

TI Asymmetric synthesis of (S)-mirtazapine: unexpected racemization through an aromatic ipso-attack mechanism

AU van der Linden, Marco; Borsboom, Judith; Kaspersen, Frans; Kemperman, Gerjan

CS Department of Process Chemistry, Organon' N. V., part of Schering-Plough, Oss, 5340 BH, Neth.

SO European Journal of Organic Chemistry (2008), (17), 2989-2997
CODEN: EJOCFK; ISSN: 1434-193X

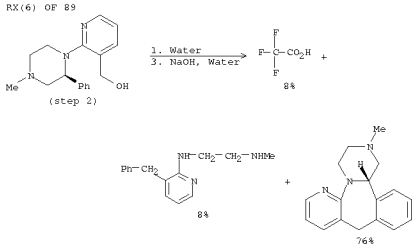
PB Wiley-VCH Verlag GmbH & Co. KGaA

DT Journal

LA English

AB An asym. synthesis of (S)-mirtazapine has been achieved from the synthesis of the racemate by using (S)-1-methyl-3-phenylpiperazine as the starting material. Unfortunately, significant racemization was encountered in the final step, which involved an electrophilic aromatic ring closure of an alc. by concentrated sulfuric acid. A significantly higher ee was observed when polyphosphoric acid (PPA) was used instead. A remarkable correlation between the amount of PPA used and the ee of the product was revealed, namely, an increase in the ee upon decreasing the amount of PPA. This trend was paralleled by the formation of an increasing amount of a side-product upon lowering the amount of PPA. The racemization and formation of a side-product can be explained by an ipso-attack mechanism during the electrophilic aromatic ring-closure reaction. This mechanism was supported by a mechanistic study using a deuterium-labeled substrate.

RX(6) OF 89

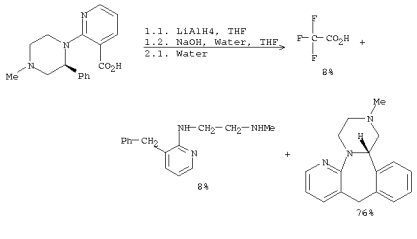


(step 2)

NOTE: regioselective, 3-Benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, enantiomeric excess depends on type and equiv. of acidic reagent and on solvent, optimization study, optimized on solvent, acidic reagent,stoichiometry,temperature and reaction time, polyphosphoric acid (PPA) used first stage
CON: STAGE(1) <140 deg C
STAGE(2) 18 hours, 130 deg C
STAGE(3) pH 8

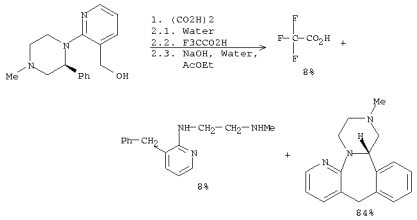
L8 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(23) OF 89 - 2 STEPS



NOTE: 2) regioselective, 3-Benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, enantiomeric excess depends on type and equiv. of acidic reagent and on solvent, optimization study, optimized on solvent, acidic reagent,stoichiometry,temperature and reaction time, polyphosphoric acid (PPA) used first stage
CON: STEP(1.1) overnight, room temperature;
room temperature -> 10 deg C
STEP(1.2) 10 deg C -> reflux; 30 minutes, reflux
STEP(2.1) <140 deg C
STEP(2.2) 18 hours, 130 deg C
STEP(2.3) pH 8

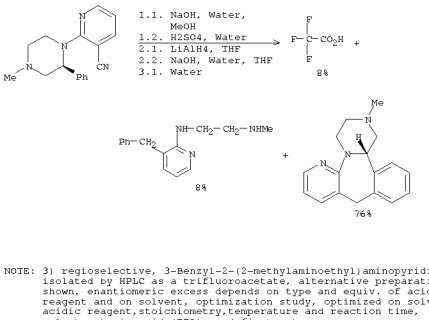
RX(34) OF 89 - 2 STEPS



NOTE: 1) no exptl. detail, 2) regioselective, 3-Benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv. of polyphosphoric acid, polyphosphoric acid (PPA) used first stage
CON: STEP(2.1) <140 deg C
STEP(2.2) 18 hours, 130 deg C

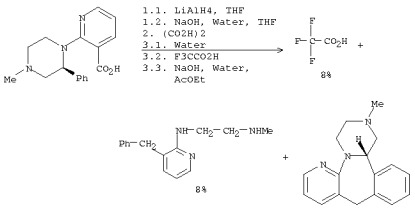
L8 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(40) OF 89 - 3 STEPS



NOTE: 3) regioselective, 3-Benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, enantiomeric excess depends on type and equiv. of acidic reagent and on solvent, optimization study, optimized on solvent, acidic reagent,stoichiometry,temperature and reaction time, polyphosphoric acid (PPA) used first stage
CON: STEP(1.1) 50 deg C; 50 deg C -> reflux; 3 days, reflux
STEP(1.2) 15 minutes, 80 deg C, pH 5.0 - 6.0
STEP(2.1) overnight, room temperature; room temperature -> 10 deg C
STEP(2.2) 10 deg C -> reflux; 30 minutes, reflux
STEP(3.1) <140 deg C
STEP(3.2) 18 hours, 130 deg C
STEP(3.3) pH 8

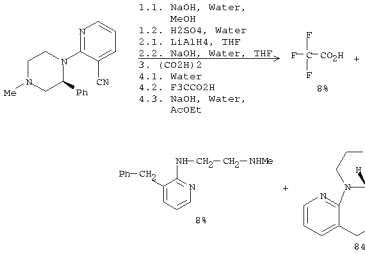
RX(44) OF 89 - 3 STEPS



L8 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

NOTE: 2) no exptl. detail, 3) regioselective, 3-Benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv. of polyphosphoric acid, polyphosphoric acid (PPA) used first stage
CON: STEP(1.1) overnight, room temperature; room temperature -> 10 deg C
STEP(1.2) 10 deg C -> reflux; 30 minutes, reflux
STEP(3.1) <140 deg C
STEP(3.2) 18 hours, 130 deg C

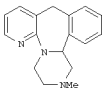
RX(45) OF 89 - 4 STEPS



NOTE: 3) no exptl. detail, 4) regioselective, 3-Benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv. of polyphosphoric acid, polyphosphoric acid (PPA) used first stage
CON: STEP(1.1) 50 deg C; 50 deg C -> reflux; 3 days, reflux
STEP(1.2) 15 minutes, 80 deg C, pH 5.0 - 6.0
STEP(2.1) overnight, room temperature; room temperature -> 10 deg C
STEP(2.2) 10 deg C -> reflux; 30 minutes, reflux
STEP(4.1) <140 deg C
STEP(4.2) 18 hours, 130 deg C

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

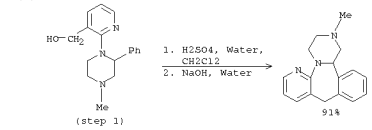
L8 ANSWER 9 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 148:379579 CASREACT
TI Improved synthesis of mirtazapine
AU Rao, D. V. N. Srinivasa; Dandala, R.; Handa, V. K.; Sivakumaran, M.; Reddy, A. V. Raghava; Naidu, A.
CS 28Department of Chemical Research, APL Research Centre, Hyderabad, 500 072, India
SO Organic Preparations and Procedures International (2007), 39(4), 399-402
CODEN: OPPIAK; ISSN: 0030-4948
PB Organic Preparations and Procedures, Inc.
DT Journal
LA English
GI



I

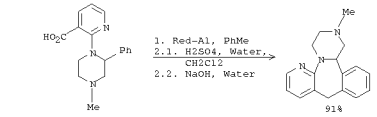
AB A known 4-step sequence for the preparation of mirtazapine (I), starting from 2-chloro-3-pyridinecarbonitrile and 1-methyl-3-phenylpiperazine, was improved at every stage. The new procedure offers advantages of higher yields, mild reaction conditions, easier work-up, and shorter reaction times.

RX(4) OF 10



CON: STAGE(1) 38 - 42 deg C; 3 hours, reflux
STAGE(2) <30 deg C, pH 10.5

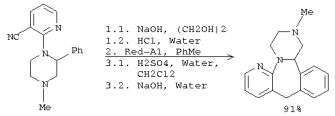
RX(7) OF 10 - 2 STEPS



CON: STEP(1.1) 2 hours, 55 - 60 deg C; 55 deg C -> 10 deg C
STEP(2.1) 38 - 42 deg C; 3 hours, reflux
STEP(2.2) <30 deg C, pH 10.5

L8 ANSWER 9 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(9) OF 10 - 3 STEPS



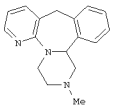
CON: STEP(1.1) 7 hours, room temperature -> 130 deg C; 130 deg C -> 30 deg C
STEP(1.2) pH 6.5 - 7
STEP(2.1) 2 hours, 55 - 60 deg C; 55 deg C -> 10 deg C
STEP(3.1) 38 - 42 deg C; 3 hours, reflux
STEP(3.2) <30 deg C, pH 10.5

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 148:239243 CASREACT
TI An improved process for the preparation of mirtazapine
IN Handa, Vijay Kumar; Rao, Divvela Venkata Naga Srinivasa; Sivakumar, Meenakshisunderam
PA Aurobindo Pharma Limited, India
SO Indian Pat. Appl., 17pp.
CODEN: INXXBQ
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN---200400794	A	20060602	2004IN-000000794	20040809
IN------205206	A1	20070629		

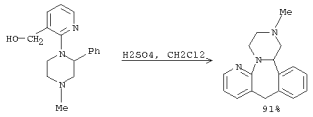
PRAI 2004IN-000000794 20040809
GI



I

AB This invention relates to an improved process for the preparation of Mirtazapine (I), which involves the cyclization of pyridine carbinol compound, with sulfuric acid in an organic solvent.

RX(1) OF 1



CON: 3 hours, 30 - 40 deg C

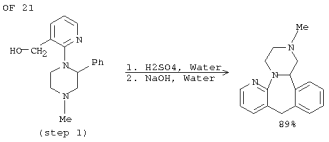
L8 ANSWER 11 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(15) OF 21 - 3 STEPS

NOTE: 3) 37.4% yield over 6 steps is from benzoylformic acid methyl ester
CON: STEP(1) 10 hours, reflux
STEP(2.1) 2.5 hours, reflux; reflux -> room temperature
STEP(2.2) 0.5 hours, room temperature
STEP(3.1) room temperature; 6 hours, 35 - 45 deg C
STEP(3.2) cooled, pH 10

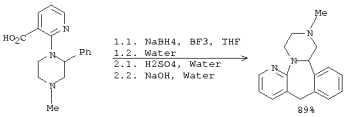
L8 ANSWER 11 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 148:168666 CASREACT
TI Synthesis of mirtazapine
AU Sun, Ping-hua; Chen, Wei-min; Guo, Jia-liang; Jin, Qian-xing; Dai, Yi
CS Faculty of Pharmacy, Jinan University, Guangzhou, 510632, Peop. Rep. China
SO Zhongguo Xinyao Zazhi (2007), 16(2), 140-142
CODEN: ZXZHA6; ISSN: 1003-3734
PB Zhongguo Xinyao Zazhi Youxian Gongsi
DT Journal
LA Chinese
AB A synthesis of mirtazapine [i.e., 1,2,3,4,10,14b-hexahydro-2-(methyl)pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine], an antidepressant agent, is reported. Mirtazapine was obtained via several steps involving cyclization, reduction, hydrolysis, etc. using Me benzoylformate as a starting material. The chemical structure of the mirtazapine was confirmed by IR, MS, and 1H-NMR. The overall yield was 37.4%. Thus, an improved synthetic procedure of mirtazapine was achievable.

RX(1) OF 21



NOTE: 37.4% yield over 6 steps is from benzoylformic acid methyl ester
CON: STAGE(1) room temperature; 6 hours, 35 - 45 deg C
STAGE(2) cooled, pH 10

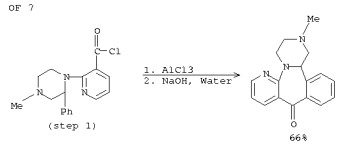
RX(10) OF 21 - 2 STEPS



NOTE: 2) 37.4% yield over 6 steps is from benzoylformic acid methyl ester
CON: STEP(1.1) 2.5 hours, reflux; reflux -> room temperature
STEP(1.2) 0.5 hours, room temperature
STEP(2.1) room temperature; 6 hours, 35 - 45 deg C
STEP(2.2) cooled, pH 10

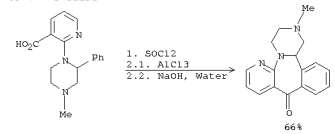
L8 ANSWER 12 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 147:211832 CASREACT
TI Synthesis of potential related substances of mirtazapine
AU Rao, Divvela V. N. Srinivasa; Dandala, Ramesh; Bharathi, Chalamakuri; Handa, Vijay Kumar; Sivakumaran, Meenakshisunderam; Naidu, Andra
CS Chemical Research Department, APL Research Centre, Hyderabad, 500 072, India
SO ARKIVOC (Gainesville, FL, United States) (2006), (15), 127-132
CODEN: AGFUAR
URL: http://www.arkat-usa.org/ARKIVOC/JOURNAL_CONTENT/manuscripts/2006/06-2187EP%20as%20published%20mainmanuscript.pdf
PB Arkat USA Inc.
DT Journal; (online computer file)
LA English
AB The synthesis of three contaminants of mirtazapine, formed during the preparation of mirtazapine bulk drug, is described. The products are 2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]pyrazino(1,2-a)pyrido[3,2-f]azepine-2-oxide, 1-(3-methylpyridyl-2)-2-phenyl-4-methylpiperazine, and 2-methyl-1,2,3,4,10,14b-hexahydro-10-oxo-benzo[c]pyrazino(1,2-a)pyrido[3,2-f]azepine. The structures of these compds. were established on the basis of spectral data (IR, 1H-NMR and MS).

RX(5) OF 7



CON: STAGE(1) 30 minutes, 5 - 10 deg C; 2 hours, 25 - 30 deg C
STAGE(2) cooled

RX(7) OF 7 - 2 STEPS



CON: STEP(1.1) room temperature -> reflux; 4 hours, reflux
STEP(2.1) 30 minutes, 5 - 10 deg C; 2 hours, 25 - 30 deg C
STEP(2.2) cooled

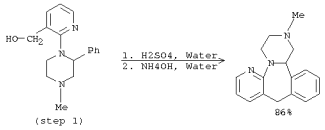
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 13 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 146:462287 CASREACT
TI Process for preparation of mirtapine
IN Kang, Yanlong; Qu, Feng; Liu, Kun
PA Beijing D-Venturepharm.T. Corp., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, ?pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN-----1939918	A	20070404	2005CN-010105688	20050930
PRAI 2005CN-010105688		20050930		

AB The present invention pertains to a process for the preparation of mirtapine, which comprises: (1) reacting 3-hydroxymethyl-2-chloropyridine and 1-methyl-3-phenyl-piperazine for 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine in an aprotic solvent at 10-180 °C; (2) cyclization of the piperazine intermediate obtained above for mirtapine. The process has the advantages of simple operation, low-cost substrates, high yield, high product quality, and hence is convenient for mass production

RX(1) OF 3



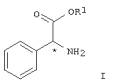
NOTE: reaction from p.5 in patent
CON: STAGE(1) room temperature -> 10 deg C; 4 hours, room temperature; 1.5 - 2.0 hours, room temperature -> 50 deg C
STAGE(2) pH 9.0

L8 ANSWER 14 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 146:380013 CASREACT
TI Preparation of optically active 1-methyl-3-phenylpiperazine and preparation of optically active mirtazapine from said piperazine derivative
IN Maeda, Hiroshi; Matsui, Kozo; Itaya, Nobushige
PA Sumitomo Chemical Company, Limited, Japan
SO PCT Int. Appl., ?2pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2007035003	A1	20070329	2006WO-JP0319625	20060925
JP--2007284416	A	20071101	2006JP-000259194	20060925
EP-----1930325	A1	20080611	2006EP-000810980	20060925
US-20090275749	A1	20091105	2008US-000067677	20080321
IN---200802019	A	20090227	2008IN-000002019	20080424
CN---101312955	A	20081126	2006CN-080043136	20080519
PRAI 2005JP-000278758		20050926		
2006JP-000079486		20060322		
2006WO-JP0319625		20060925		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

OS MARPAT 146:380013
GI

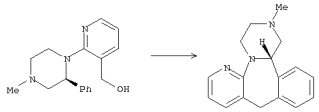


I

AB Optically active 1-methyl-3-phenylpiperazine is prepared by reaction of MeN(Z1)CH2CO2H [Z1 = protecting group for amino group] with optically active phenylglycine derivative I [R1 = (un)substituted alkyl, (un)substituted cycloalkyl, (un)substituted aralkyl; the carbon atom with the asterisk is an asym. carbon atom], followed by removal of the Z1 protecting group, cyclization, and reduction The process for producing optically active mirtazapine from I is also disclosed. Thus, hydrogenation of (S)-N-(N-benzyloxycarbonylsarcosyl)phenylglycine Me ester [prepared from N-benzyloxycarbonylsarcosine and (S)-phenylglycine Me ester hydrochloride] gave (S)-N-sarcosylphenylglycine Me ester (II); cyclization of II gave (S)-1-methyl-3-phenylpiperazine-2,5-dione (III); reduction of III gave (S)-1-methyl-3-phenylpiperazine.

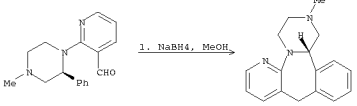
L8 ANSWER 14 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(10) OF 42



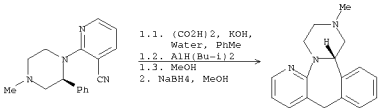
NOTE: literature preparation

RX(18) OF 42 - 2 STEPS



NOTE: 2) literature preparation
CON: STEP(1.1) 30 minutes, 5 deg C; 30 minutes, 5 deg C

RX(30) OF 42 - 3 STEPS

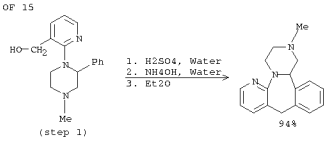


NOTE: 3) literature preparation
CON: STEP(1.1) 1 hour, 25 - 30 deg C
STEP(1.2) -67 - -52 deg C; 2 hours, -64 - -44 deg C
STEP(2.1) 30 minutes, 5 deg C; 30 minutes, 5 deg C

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

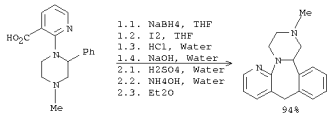
L8 ANSWER 15 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 146:100636 CASREACT
TI Synthesis of antidepressant-mirtazapine
AU Zhang, Tao; Wu, Fan-hong
CS School of Chemistry and Pharmaceutics, East China University of Science and Technology, Shanghai, 200237, Peop. Rep. China
SO Huadong Ligong Daxue Xuebao, Ziran Kexueban (2006), 32(3), 318-320, 326
CODEN: HLIXEV; ISSN: 1006-3080
PB Huadong Ligong Daxue Xuebao Bianjibu
DT Journal
LA Chinese
AB Mirtazapine [i.e., 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine] was prepared by a seven-step reaction, namely nucleophilic ring-opening reaction, chlorination, cyclization, nucleophilic substitution, hydrolysis, reduction and cyclization from styrene oxide and N-methylethanolamine as the starting materials, with overall yield of 22. 6%. The structure of mirtazpine was confirmed by 1H-NMR (H1-NMR) and MS(mass spectrum), and the purity was 99.79% by HPLC.

RX(1) OF 15



NOTE: 23% overall yield from 2-phenyl-Oxirane
CON: STAGE(1) room temperature; 4 hours
STAGE(2) cooled, basify

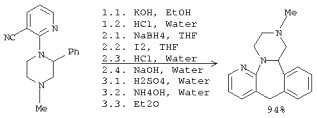
RX(9) OF 15 - 2 STEPS



NOTE: 2) 23% overall yield from 2-phenyl-Oxirane
CON: STEP(1.1) room temperature
STEP(1.2) 30 minutes, 0 - 5 deg C; 1 hour, room temperature; 5 hours, reflux
STEP(1.3) 30 minutes, room temperature
STEP(1.4) room temperature, basify
STEP(2.1) room temperature; 4 hours
STEP(2.2) cooled, basify

L8 ANSWER 15 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

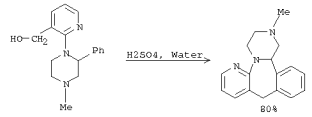
RX(13) OF 15 - 3 STEPS



NOTE: 3) 23% overall yield from 2-phenyl-Oxirane
CON: STEP(1.1) room temperature -> 100 deg C; 32 hours, 100 deg C; cooled
STEP(1.2) neutralized
STEP(2.1) room temperature
STEP(2.2) 30 minutes, 0 - 5 deg C; 1 hour, room temperature; 5 hours, reflux
STEP(2.3) 30 minutes, room temperature
STEP(2.4) room temperature, basify
STEP(3.1) room temperature; 4 hours
STEP(3.2) cooled, basify

L8 ANSWER 16 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)
CHCl3 extn. (which leads to impurities), crystn. from ether (difficult on a large scale), and recrystn. from petroleum ether 40-60 (also difficult to handle on a large scale). Still other methods add solid II to H2SO4, also disadvantageous in an industrial setting. Moreover, the prior art methods do not always lead to pharmaceutical grade I. Six examples of the invention process are given. For instance, 32.2 kg.of 96.10% H2SO4 was added to a mixt. of 7.0 kg II and 3.5 kg deionized H2O at <80°, and the mixt. was stirred for 2 h at 75-80°. The mixt. was cooled to room temp., dild. with cold water at <25°, and distributed between PhMe and 26% NH4OH (pH to 8.9-9.3). After repeated extn. with PhMe, the PhMe phases were combined, washed with H2O, dried with NaSO4, filtered, decolorized twice with active C, filtered, and evapd. at >40°. I was crystd. from the residue using EtOAc, then filtered, recrystd. from EtOAc, and dried in vacuo (40-60°, ≤100 mmHg) to give 4.7 kg product (72% yield) with HPLC purity 99.7%, PhMe below detection limit of 100 ppm, and EtOAc 299 ppm.

RX(1) OF 1



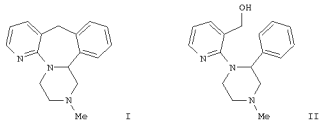
NOTE: optimization study, workup
CON: STAGE(1) 0.33 hours, 20 - 60 deg C; 60 deg C; 7 hours, 60 deg C

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 144:171016 CASREACT
TI Improved process for the manufacture of mirtazapine by acid-induced ring closure of an alcohol precursor in selected solvents
IN Arnalot Aguilar, Carmen
PA Medichem, S.A., Spain
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2006008302	A2	20060126	2005WO-EP0053493	20050719
	WO--2006008302	A3	20060413		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	ES-----2246161	A1	20060201	2004ES-000001804	20040722
	ES-----2246161	B1	20070401		
	AU--2005263761	A1	20060126	2005AU-000263761	20050719
	CA-----2572831	A1	20060126	2005CA-002572831	20050719
	EP-----1768980	A2	20070404	2005EP-000778967	20050719
	EP-----1768980	B1	20081126		
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	BR--2005013571	A	20080506	2005BR-000013571	20050719
	AT------415401	T	20081215	2005AT-000778967	20050719
	PT-----1768980	E	20090302	2005PT-000778967	20050719
	ES-----2318520	T3	20090501	2005ES-000778967	20050719
	AR-------50004	A1	20060920	2005AR-000103022	20050721
	IN---2007000175	A	20070803	2007IN-000000175	20070108
	KR--2007053697	A	20070525	2007KR-007001149	20070117
	MX--2007000725	A	20070523	2007MX-000000725	20070118
	NO--2007000776	A	20070411	2007NO-000000776	20070209
	US-20080207896	A1	20080828	2007US-000630505	20071228
PRAI	2004ES-000001804		20040722		
	2005WO-EP0053493		20050719		

GI



AB An improved process for manufacture of the antidepressant mirtazapine (I) is reported. The process involves ring cyclization of alc. II in selected solvents, and gives mirtazapine on an industrial scale, for pharmaceutical use, in crystalline and anhydrous forms. Suitable solvents include halogenated hydrocarbons (especially CH2Cl2), hydrocarbons, and water. Some prior art methods involve addition of concentrated H2SO4 to solid II, giving inefficient stirring and difficult reaction control. Some prior methods also involve

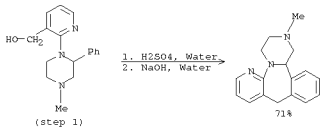
=> d bib abs crd l7 tot

L7 ANSWER 1 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 143:7729 CASREACT
TI Preparation of mirtazapine antidepressant
IN Yang, Yushe; Guo, Baishu; Chen, Kaixian; Ji, Ruyun
PA Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 9 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN-----1429819	A	20030716	2001CN-000145561	20011229
PRAI 2001CN-000145561		20011229		

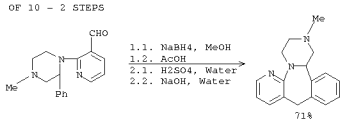
AB The method comprises substituting 1-methyl-3-phenylpiperazine with 2-chloro-3-cyanopyridine in DMF or DMSO to obtain 2-(3-cyano-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with Raney Ni/NaH2PO2 in water-acetic acid-pyridine mixed solvent at 50-60° to obtain 2-(3-formyl-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with NaBH4 or KBH4 in alc. at room temperature, cyclizing with concentrated H2SO4 at 50-60°, and recrystg. in petroleum ether-ethanol-water.

RX(4) OF 10



CON: STAGE(1) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STAGE(2) 0 deg C, pH 10

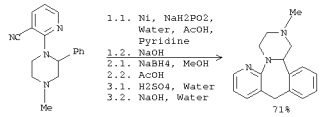
RX(7) OF 10 - 2 STEPS



CON: STEP(1.1) 2 hours, room temperature
STEP(2.1) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STEP(2.2) 0 deg C, pH 10

L7 ANSWER 1 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(9) OF 10 - 3 STEPS

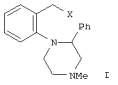


CON: STEP(1.1) 5 hours, 50 - 60 deg C
STEP(1.2) pH 10
STEP(2.1) 2 hours, room temperature
STEP(3.1) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STEP(3.2) 0 deg C, pH 10

L7 ANSWER 2 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 142:134623 CASREACT
TI Preparation of enantiomerically pure (S)-mirtazapine
IN Wieringa, Johannes Hubertus; Van De Ven, Adrianus Antonius Martinus; Kemperman, Gerardus Johannes
PA Akzo Nobel N.V., Neth.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2005005410	A1	20050120	2004WO-EP051357	20040705
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU--2004255874	A1	20050120	2004AU-000255874	20040705
AU--2004255874	B2	20101028		
CA-----2531165	A1	20050120	2004CA-002531165	20040705
EP-----1656365	A1	20060517	2004EP-000741958	20040705
EP-----1656365	B1	20090617		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN-----1820000	A	20060816	2004CN-080019489	20040705
CN---100558722	C	20091111		
BR--2004012447	A	20060919	2004BR-000012447	20040705
NZ------544360	A	20080530	2004NZ-000544360	20040705
SG------144914	A1	20080828	2008SG-000005127	20040705
JP--2009513537	T	20090402	2006JP-000518216	20040705
RU-----2352566	C2	20090420	2006RU-000103992	20040705
AT------433965	T	20090715	2004AT-000741958	20040705
PT-----1656365	E	20090901	2004PT-000741958	20040705
ES-----2327123	T3	20091026	2004ES-000741958	20040705
IL------172549	A	20101031	2004IL-000172549	20040705
LT--------5382	B	20061127	2005LT-000000107	20051212
HR--2005001019	A2	20060228	2005HR-000001019	20051222
NO--2005006175	A	20060123	2005NO-000006175	20051223
ZA--2006000019	A	20070131	2006ZA-000000019	20060103
US--20060229300	A1	20061012	2006US-000564193	20060106
IN---200600083	A	20070831	2006IN-000000083	20060106
IN------229885	A1	20090327		
MX--2006000325	A	20060330	2006MX-000000325	20060109
KR--2006056315	A	20060524	2006KR-007000511	20060109
LV-------13441	B	20060820	2006LV-000000021	20060210
HK-----1086841	A1	20090821	2006HK-000109133	20060817
PRAI 2003EP-000102095		20030710		
2004WO-EP051357		20040705		

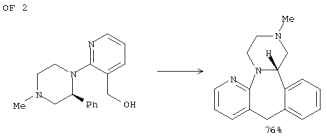
OS MARPAT 142:134623
GI



AB (S)-Mirtazapine was prepared using a ring closure reaction of (S)-pyridylpiperazine I (X = leaving group) using an acid and an organic solvent or in the absence of solvent. For example, (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine, I (X = OH), was dissolved in N-methylpyrrolidinone and polyphosphoric acid was added.

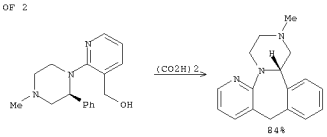
L7 ANSWER 2 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)
The title compd. was obtained in 68% yield with 99.2% ee.

RX(1) OF 2



NOTE: optimization study, stereoselective, polyphosphoric acid was used
CON: 18 hours, room temperature -> 130 deg C

RX(2) OF 2



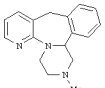
NOTE: stereoselective, polyphosphoric acid was used
CON: 18 hours, room temperature -> 130 deg C

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 138:304301 CASREACT
TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
IN Singer, Claude; Liberman, Anita; Finkelstein, Nina
PA Israel
SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 552,485.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US-20030069417	A1	20030410	2002US-000206344	20020729
CN-----1679586	A	20051012	2005CN-010004288	20000418
CN-----1680374	A	20051012	2005CN-010004289	20000418
CN-----1680365	A	20051012	2005CN-010004290	20000418
US-20010051718	A1	20011213	2001US-000900646	20010706
US-----6545149	B2	20030408		
US-20030088094	A1	20030508	2002US-000283093	20021030
US-----6576764	B2	20030610		
US-20030120068	A1	20030626	2003US-000348757	20030123
US-20030135043	A1	20030717	2003US-000368441	20030220
US-20040176591	A1	20040909	2004US-000800918	20040316
AU---2005201117	A1	20050407	2005AU-000201117	20050315

PRAI 1999US-00130047P 19990419
2000US-00182745P 20000216
2000US-000552485 20000418
2000AU-000043577 20000418
2000CN-000807574 20000418
2001US-000900646 20010706
2002US-000283093 20021030
2003US-000368441 20030220
OS MARPAT 138:304301
GI


I


II

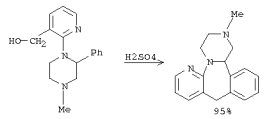

III


IV

AB Mirtazapine (I) was prepared by reacting substituted pyridine II [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound III [R3 = Cl, F, Br, I] followed by treating the resulting piperazine IV with ring closing reagent, such as H2SO4. The mirtazapine intermediate IV (R1 = CN) with KOH at a temperature of at least about 140°C. New processes for recrystn. of I form crude mirtazapine are also disclosed. The present invention also relates to crystalline adducts of mirtazapine and water, preferably containing up to about 3.5% by weight water, pharmaceutical compns. containing the crystalline adducts, and methods of treating depression by administering such compns.

L7 ANSWER 3 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(3) OF 4



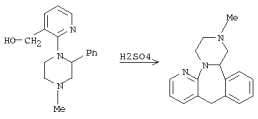
NOTE: alternative prepn. gave lower yields
CON: 6 hours, 35 deg C

L7 ANSWER 4 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 137:216962 CASREACT
TI Methods for the preparation of mirtazapine intermediates
IN Metzger, Leonid; Wizel, Shlomit
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO--2002070513	A1	20020912	2002WO-US0004340	20020214
WO--2002070513	A9	20021121		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA-----2438446	A1	20020214	2002CA-002438446	20020214
AU--2002247130	A1	20020919	2002AU-000247130	20020214
US-20020165238	A1	20021107	2002US-000073960	20020214
US-----6774230	B2	20040810		
EP-----1370549	A1	20031217	2002EP-000714893	20020214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP--2005501808	T	20050120	2002JP-000569833	20020214
IN---200300777	A	20050429	2003IN-000000777	20030822

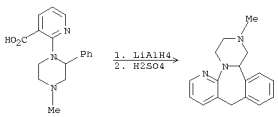
PRAI 2001US-00272699P 20010301
2002WO-US0004340 20020214
AB The preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate (I) and other mirtazapine intermediates are described. These compds. are particularly useful in the preparation of mirtazapine. Thus, 1-(3-cyano-2-pyridyl)-4-methyl-2-phenylpiperazine was hydrolyzed with aqueous KOH, neutralized with HCl and the precipitate washed with water to give I whose crystal structure is reported.

RX(4) OF 7



NOTE: no exptl.

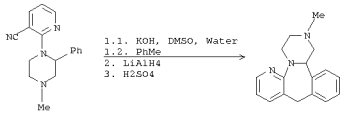
RX(6) OF 7 - 2 STEPS



NOTE: 1) no exptl., 2) no exptl.

L7 ANSWER 4 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(7) OF 7 - 3 STEPS



NOTE: 2) no exptl., 3) no exptl.

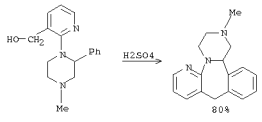
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 136:401782 CASREACT
TI Process for the manufacture of anhydrous, solvent-free mirtazapine crystals
IN Maeda, Chiharu; Yoshikawa, Sadanobu; Iishi, Eiichi
PA Sumika Fine Chemicals Co., Ltd., Japan
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP-----1209159	A2	20020529	2001EP-000111102	20010508
EP-----1209159	A3	20030305		
EP-----1209159	B1	20041117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US-20020065413	A1	20020530	2001US-000842871	20010427
US-----6660730	B2	20031209		
AU--2001040301	A	20020606	2001AU-000040301	20010430
AU------781974	B2	20050623		
CA-----2346195	A1	20020527	2001CA-002346195	20010502
AT------282616	T	20041215	2001AT-000111102	20010508
PT-----1209159	E	20050131	2001PT-000111102	20010508
ES-----2231340	T3	20050516	2001ES-000111102	20010508
JP--2002220390	A	20020809	2001JP-000291863	20010925
JP-----4321983	B2	20090826		
IL------146548	A	20070819	2001IL-000146548	20011119

PRAI 2000JP-000359891 20001127
AB Methods for producing anhydrous mirtazapine crystals that are either (1) substantially free of lower alc. insolubles or (2) substantially free of residual solvent, and which have an average particle diameter of from 10-50 μm, are described where: one filters a lower alc. (e.g., methanol) solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and crystallizing the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.

RX(1) OF 1



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

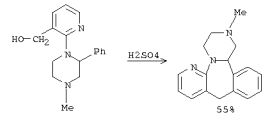
L7 ANSWER 6 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 136:369741 CASREACT
TI A novel method for preparation of piperazine and its derivatives
IN Sebastian, Sonny; Patel, Hetal Virendra; Thennati, Rajamannar
PA Sun Pharmaceutical Industries Ltd., India
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2002038552	A1	20020516	2001WO-IN0000129	20010629
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IN------190478	A1	20030802	2000IN-000000994	20001107
AU--2001078669	A	20020521	2001AU-000078669	20010629
BE------1013317	A6	20011106	2001BE-000000513	20010727
CH-------692342	A5	20020515	2001CH-000001428	20010802
US--20020095038	A1	20020718	2001US-000037309	20011025
US-----6603003	B2	20030805		
IN---200200411	A	20040228	2002IN-000000411	20020506

PRAI 2000IN-000000994 20001107
2001WO-IN0000129 20010629
OS MARPAT 136:369741
GI

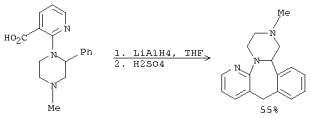
AB Compds. I [R = H, C1-6 alkyl, phenyl-C1-4 alkyl; R1 = H, Me, (un)substituted phenyl; R2 = H, Me, fluoromethyl] useful as starting materials for preparation of pharmaceutically active compds. are prepared by reacting R1COCO2R with H2NCHECHR2NHR to give 3,4-dehydropiperazine-2-one and its derivs., followed by reacting with a reducing agent to yield I. Thus, 1-methyl-3-phenylpiperazine was prepared and used as starting material for preparation of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine.

RX(7) OF 28

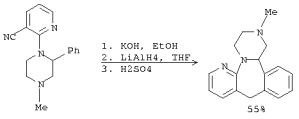


L7 ANSWER 6 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(13) OF 28 - 2 STEPS



RX(21) OF 28 - 3 STEPS



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 133:321900 CASREACT
TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
IN Singer, Claude; Liberman, Anita; Finkelstein, Nina
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2000062782	A1	20001026	2000WO-US0010357	20000418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA-----2368815	A1	20001026	2000CA-002368815	20000418
AU--2000043577	A	20001102	2000AU-000043577	20000418
AU------781221	B2	20050512		
TR--2001003028	T2	20020121	2001TR-000003028	20000418
EP-----1178805	A1	20020213	2000EP-000923457	20000418
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU--2002008839	A2	20020828	2002HU-000000839	20000418
HU--2002000839	A3	20030528		
JP--2004500324	T	20040108	2000JP-000611918	20000418
CN-----1679586	A	20051012	2005CN-010004288	20000418
CN-----1680374	A	20051012	2005CN-010004289	20000418
CN-----1680365	A	20051012	2005CN-010004290	20000418
ZA--2001008220	A	20021205	2001ZA-000008220	20011005
IN---200101253	A	20050819	2001IN-000001253	20011011
IN------203178	A1	20070511		
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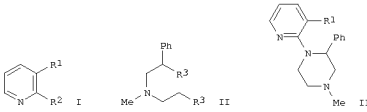
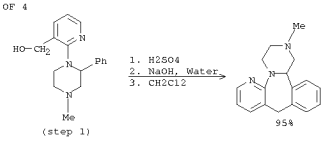


AB Mirtazapine, useful in treating depression (no data), was prepared by reacting pyridine I [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound II [R3 = Cl, F, Br, I] followed by treating the resulting piperazine III

L7 ANSWER 7 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)
with H2SO4. The mirtazapine intermediate 1-(3-carboxypyridly-2)-4-methyl-2-phenylpiperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine with KOH at a temp. of at least about 130°C. The present invention also relates to new processes for recrystn. of mirtazapine form crude mirtazapine.

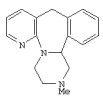
RX(1) OF 4



(step 1)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

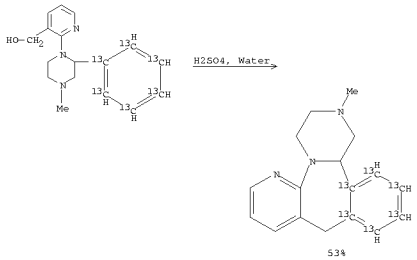
L7 ANSWER 8 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 112:139001 CASREACT
TI The synthesis of Org 3770 labeled with tritium, carbon-13 and carbon-14
AU Kaspersen, Frans M.; Van Rooij, Fons A. M.; Sperling, Eric G. M.; Wieringa, Joop H.
CS Scl. Dev. Group, Organon Int. BV, Oss, 5340 BH, Neth.
SO Journal of Labelled Compounds and Radiopharmaceuticals (**1989**), 27(9), 1055-68
CODEN: JLCRD4; ISSN: 0362-4803
DT Journal
LA English
GI



I

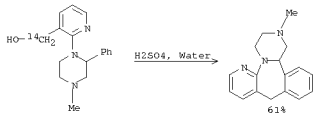
AB The syntheses of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (Org 3770, I) labeled with 3H (and 2H), 13C and 14C are described. Tritiated I was prepared either by exchange under alkaline conditions with tritiated water or catalytic reductive denalogenation of a chloro analog with 3H2. 13C-labeled material was obtained in a 7-step synthesis starting from 13C-labeled benzene, whereas I-14C was prepared in a 3-step synthesis starting with 14CO2.

RX(10) OF 118

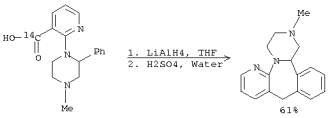


L7 ANSWER 8 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

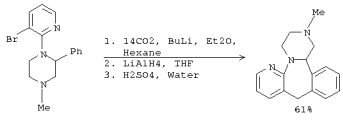
RX(15) OF 118



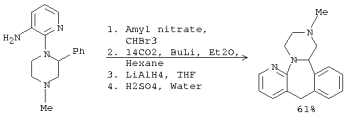
RX(30) OF 118 - 2 STEPS



RX(54) OF 118 - 3 STEPS



RX(55) OF 118 - 4 STEPS



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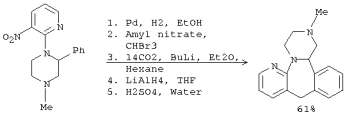

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L7             8 L5-6
L8            16 L4 NOT L7


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